

**REMARKS**

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary attached to the April 6, 2005 Office Action correctly noted that claims 21 to 41 were pending in this application. By the present amendment, claims 22 and 33 have been canceled without prejudice or disclaimer to the subject matter disclosed therein. Additionally, claims 42 to 50 have been added to more fully protect the subject invention. Claims 23 to 41 have also been amended herein. Support for the claim amendments and added claims and discussion of the issues raised in the Office Action are set out below.

**Support for Claim Amendments:**

Claims 23 to 31, and 33 to 41 have been amended to correct their dependencies which were clearly inappropriate, as they depended previously from a cancelled claim. Claim 32 has been amended to correct an obvious error in the wording at the end of the claim, and to make that wording consistent with the first line of the claim. Thus, no new matter has been added.

**Support for Added Claims:**

Claim 42 has been added to protect a further embodiment of the invention, namely a method for inhibiting activation of neutrophils in a mammal. Support for this claim can be found throughout the specification as filed. At the priority date of the subject application, August 13, 1996, those of ordinary skill in the art understood

that activation of neutrophils involved their active migration to sites of inflammation and an increase in their production of superoxide. As discussed at page 3, lines 9 to 12 of the specification as filed, it had been observed that salivary endocrine secretions could modulate the immune system, for example neutrophil function.

The specification as filed, at pages 10 to 11, also teaches that the peptides of the invention are useful for the treatment of any disorder ameliorated by down-regulation of neutrophil function.

In the specification as filed, experiments are described which examined the effects of the peptides of the invention on such indicia of neutrophil activation as neutrophil migration towards a model inflammatory stimulus and neutrophil production of superoxide.

At page 23 of the specification as filed, in Example 4, it is described that SGP-T treated animals showed inhibition of neutrophil migration which was dose-dependent.

A further indication of the attenuation of neutrophil activation brought about by the SGP-T treatment is the observation in Example 4 that neutrophils from treated animals remained capable of superoxide generation in vitro after removal from the animal, (see page 23, line 37 to page 24, line 3 and Figure 5 of the specification) indicating that their activation had been inhibited while in vivo.

In contrast, the neutrophils from untreated animals had been activated in vivo and their superoxide generation ability exhausted, so that no superoxide generation was seen in vitro after they were harvested – see page 23, lines 33 to 37.

In Example 5, pages 24 to 25, SGP-T at low, pharmacological doses (<1μm) gave inhibition of superoxide production. The stimulation of superoxide production

seen at 10 µm and 20 µm SGP-T was likely due to supra-pharmacological stimulation at these high doses, a biphasic relationship often observed with ligand-receptor interactions in biological systems.

It is submitted that those of ordinary skill in the art would appreciate that the data reported in the application showed inhibition of neutrophil activation by the peptides of the invention.

Dependent claims 43 to 45, dependent on claim 42, are comparable to the dependent claims already existing in the application.

New claims 46 and 47, dependent respectively on claims 21 and 32, have been added to more fully protect the invention and define the peptide as Phe-Glu-Gly-Gly-Gly. Support for this peptide (FEGGG) can be found in Tables 2 and 3.

Claims 48, 49 and 50 have been added to provide a dependent claim from each independent claim, directed to a sub-group of the peptides included in the independent claims. Claims 48, 49 and 50 further define X<sup>2</sup> as an acidic amino acid residue, R<sup>1</sup> as NH<sub>2</sub>- and R<sup>2</sup> as a sequence of 1 to 3 amino acid residues which are the same or different and are aliphatic amino acid residues. Support for these amendments can be found in Table 2 of the application as filed where active peptides are demonstrated which have these features.

Accordingly, no new matter has been added.

**Rejection Under 35 U.S.C. § 112, First Paragraph:**

The Examiner has rejected claims 21 to 41 under 35 USC, §112, first paragraph, arguing that while the specification enables the treatment of inflammation with the peptide FEG and the specific tripeptides claimed in U.S.P. 6,586,403, it

does not reasonably provide enablement for any peptide of the formula R<sub>1</sub>-X<sub>1</sub>-X<sub>2</sub>-R<sub>2</sub>, as defined in the claims, for the same purpose or for the prevention of inflammatory reactions or the prevention of neutrophil infiltration into an inflammatory site. This rejection is respectfully traversed.

The Examiner has set out the factors to be considered with respect to enablement, as described in In re Wands, 8 U.S.P.Q 2d 1400 (Fed. Cir. 1988). Applicants review below the Examiner's analysis of these factors as they relate to the present invention and provide their response, dealing with each factor in turn.

**(1) The Nature of the Invention**

The invention relates to the identification of a group of peptides which "modulate anaphylactic, endotoxic and inflammatory reactions" (page 1, lines 5 to 7 of specification), and which may be used for "the treatment of inflammation or any disorder ameliorated by down regulation of neutrophil function."

**(2) The State of the Prior Art; and**

**(3) The Relative Skill of Those in the Art**

As noted by the Examiner, the relative skill of those in the art is high.

**(4) The Predictability or Unpredictability of the Art**

The Examiner first discussed the predictability of activity of peptides and referred to papers by Ngo et al. (The Protein Folding Problem and Tertiary Structure Prediction, (1994), Ed. Merz et al. pp. 491 to 495) and Rudinger, J. (Peptide Hormones, (1976) Ed. Parsons, J.A., pp. 1 to 7).

Ngo et al. discusses in this paper the predictability of protein folding, i.e., the prediction of tertiary structure in chains of 20 or more amino acids. The peptides of

the present invention are at most 8 amino acids in length and do not have tertiary structure. Rudinger does discuss sequence and conformation in peptides but comments significantly on the importance for conformational stability not just of the amino acids of the hormone-receptor site but of "groups widely separated in the linear sequence" (page 4). Clearly, this author also is considering peptides of a considerable length, such that amino acid groups are widely separated. Such arguments do not apply to peptides containing 3 to 8 amino acids, such as the peptides of the invention.

Furthermore, the applicants have presented guidance concerning the structure-activity relationships of the peptides of the invention, for example in Examples 6 to 9 described in the specification and the Results presented in Tables 2, 3 and 4, where activity was assessed for each of a series of analogues so as to provide guidance to the skilled practitioner and support the enablement of the claimed genus of peptides.

The Examiner has also questioned the enablement of "prevention" of an inflammatory reaction. It is submitted that the Examiner has adopted an overly rigid interpretation of the word "prevention", interpreting it to mean absolute and permanent prevention. It is submitted that the proper standard for interpreting "prevention" is as one of skill in the art would expect the term to be interpreted, *i.e.*, "a reasonable degree of prevention for a time sufficient to confer a benefit on a subject".

**(5) The Breadth of the Claims**

It is submitted that the breadth of the claims is fairly and reasonably based on the information contained in the application regarding the peptides of the invention and their effects. A number of peptide analogues of the peptides FEG and feG have been examined for their structure activity relationships in Examples 6 to 9, as discussed above, giving support for claims directed to the genus of peptides defined in the independent claims. Additionally, the dependent claims of the application are directed to various sub-groups of that genus, again fully supported by the information contained in the application as filed. Furthermore, certain dependent claims, such as claims 29, 30, 40, 41 and 44 to 47 are directed to individual peptides or groups of two or three peptides which are fully described in the application.

The examples also show that the peptides of the invention are effective in modulating inflammatory reactions caused, for example, by exposure of a sensitised subject to an allergen or by an endotoxic reaction.

Furthermore, the examples show that the peptides of the invention have a profound inhibitory effect on the activation and therefore function of neutrophils and are therefore useful for the treatment of disorders ameliorated by the down regulation of neutrophils and for inhibition of neutrophil migration.

**(6) The Amount of Direction or Guidance Presented; and**

**(7) The Presence or Absence of Working Examples**

The Examiner has argued that the specification fails to provide ample guidance that any peptide of the claimed formula will be effective in treating,

reducing or preventing anaphylactic reactions, asserting that the examples utilise only the peptide FEG.

Firstly, the present claims are directed to treating or preventing an inflammatory reaction, inhibiting or preventing neutrophil infiltration into an inflammatory site or inhibiting activation of neutrophils. Claims to reducing an anaphylactic reaction or treating anaphylactic hypotension using the peptides of the invention have already been granted in U.S.P. 6,852,697.

It is not correct that the examples utilise only FEG. As discussed above, Examples 6 to 9 and Tables 2, 3, and 4 show the structure-activity relationships of a wide variety of analogues of FEG, thus providing numerous working examples and much guidance for one skilled in the art.

The Examiner again referred to teachings of Ngo et al. and Rudinger. As also discussed above, these teachings are relevant to longer amino acid chains with tertiary structure but not to short peptides such as those of the invention.

The Examiner also asserted that the specification fails to provide any guidance that the peptides of the invention are effective in preventing an inflammatory response, for example in rheumatoid arthritis or inflammatory bowel disease. It is respectfully submitted that the application does demonstrate that the peptides of the invention are effective in preventing an inflammatory response. The applicants' position regarding "prevention" has been discussed above.

The Examiner referred to Ex parte Sudilovsky and asserted that the situation is similar with respect to the present application.

It appears from the Examiner's quote from Ex parte Sudilovsky that that application merely described a group of compounds and how to formulate them for

administration and nothing more, no working examples. In contrast, the present application is replete with working examples regarding inhibition or prevention of anaphylactic reactions, and by analogy inflammatory reactions.

The Examiner further asserts, at page 6 (bottom) to page 7 of the Official Action, that the subject disclosure has not provided evidence of record of a representative set of compounds corresponding to the [claimed] formula and possessing the claimed activity and that undue experimentation would be required to practice the claimed invention.

It is clear from the Examples discussed above which look at structure-activity relationships that the applicants have provided evidence of a representative set of compounds possessing the claimed activity and the formula defined in the claims is based on this very evidence.

#### **(8) The Quantity of Experimentation Necessary**

The Examiner asserted that undue experimentation would be required given the level of unpredictability in determining peptide activity based on structure.

As discussed fully above, the evidence the Examiner relies on for this asserted unpredictability is relevant to much longer amino acid chains than the short peptides of the invention. Furthermore, the application gives guidance on the analogues which can be expected to retain activity, as reflected in the formula defined in the claims. Furthermore, screening experiments of the type described in the Examples of the subject application with respect to structure/activity relationships are easily and simply carried out by those of ordinary skill in the art. Armed with this

information, it would be routine for one of skill in the art to practice the invention without any undue experimentation.

In view of the above, withdrawal of the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

**Double Patenting Rejection**

The Examiner has rejected claims 21 to 41 under the judicially created doctrine of obviousness-type double patenting as purportedly being unpatentable over claims 1 to 32 of U.S.P. 6,586,403.

The Examiner has argued that U.S.P. 6,586,403 claims various treatment methods effected by administering the same peptides that are claimed in claims 29 to 30 of the present application.

The Examiner is incorrect. All of the claims of U.S.P. 6,586,403 are directed to peptides all of which are amidated – see, for example, claim 1 “wherein Y is NH<sub>2</sub>” – and to methods employing such amidated peptides.

In contrast, the peptides of the claims of the subject application are not amidated.

It is submitted that the claims of U.S.P. 6,586,403 do not render the present claims obvious. Thus, withdrawal of this obviousness-type double patenting rejection is respectfully requested.

**Different Inventors, Common Assignee**

The Examiner has rejected claims 21 to 41 as not patentably distinct from certain of the claims of commonly assigned U.S.P. 6,586,403.

As discussed in the immediately preceding section of this response, applicants submit that U.S.P. 6,586,403 does not render the claims of the present application obvious. The Examiner is incorrect that the peptides claimed in U.S.P. 6,586,403 are the same as the peptides of the present invention.

The Examiner also notes that U.S.P 6,586,403 would form the basis for a rejection of the claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g).

It is respectfully submitted that U.S.P. 6,586,403 does not qualify as prior art under any statute, as it has a filing date of July 20, 2000. The instant application is a divisional of U.S. 09/051,395 which has a U.S. filing date of August 5, 1998 and is a 371 of PCT/CA97/00568 which has a filing date of August 13, 1997, and claims priority under § 119 from United Kingdom application GB 9617021.2 filed August 13, 1996.

It is therefore submitted that no showing of common ownership at the time that the invention of this application was made should be required.

### Conclusion

In summary, the applicants submit that the claims of this application are fully enabled by the description as filed and are patentable over U.S.P. 6,586,403.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would

Attorney's Docket No. 024916-013  
Application No. 10/773,229  
Page No. 20

telephone the undersigned attorney concerning such questions so that prosecution  
of this application may be expedited.

Respectfully submitted,

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